OLGU SUNUMU

[1]Recep EROZ, PhD
[1]Mustafa DOGAN, MD
[1]Huseyin YUCE, PhD
[2]Recep OZMERDIVENLI,PhD

[1] Duzce University Medical Faculty,Department of Medical Genetics, Duzce
[2] Duzce University Medical Faculty, Department of Physiology, Duzce

Yazışma Adresi:
Recep Eroz
Duzce University Medical Faculty, Department of Medical Genetics, Duzce (81820),
Tel: +90 380 5421128,
E-mail: eroz38r@hotmail.com

Konuralp Tıp Dergisi
e-ISSN1309–3878
konuralptipdergi@duzce.edu.tr
konuralptipdergisi@gmail.com
www.konuralptipdergi.duzce.edu.tr

MEFV Geni 761_764dupCCGC p.Asn256Argfs70, c.761_764dupCCGC Mutasyonlu Türkiyeden Bir Aile, Onların Klinik Özellikleri ve Literatür Taraması

ÖZET
Ailesel Akdeniz Ateşi (FMF) primer olarak Musevi, Ermeni, Türk ve Arap populasyonunu etkileyen otozomal resesif geçişli bir otoenflamatuvar bir hastalıktır. FMF, Mediterranean Fever (MEFV) geni kromozom 16p13.3 bölgesinde yerleşen, 10 ekzondan oluşan hastalıktan sorumlu bir gendir. Klinik olarak FMF tanısı almış total 5 kişiden oluşan bir Türk ailesi incelendi. MEFV geninin tüm ekzom sekans analizi aile bireyleri için yapıldı. Bizim sonuçlarımıza göre, MEFV geninin 2. Ekzonunda bir 761_764dupCCGC (p.Asn256Argfs70,c.761_764dupCCGC) duplikasyon mutasyonu tespit edildi. Proband, onun erkek kardeşi, kız kardeşi ve babası bu mutasyonu taşımasına rağmen, probandın annesi hiçbir mutasyon taşımıyordu. Literatürde bu mutasyonlu yalnızca bir hasta bildirilmiştir (HGMD no: CI055758) ve hastanın kliniğiyle ilgili sınırlı veri paylaşılmıştır. Probandın aile öyküsü yoktu fakat göğüs ve karın ağrısı vardı. İlginç olarak bu mutasyonlu diğer aile üyeleri FMF'in klinik bulgularına sahip değillerdi. PolyPhen-2 ve Mutation Taster bioinformatics programlarına göre bu duplikasyon patojenik olarak görünüyordu. 761_764dupCCGC mutasyonu hakkında daha açık bilgi elde edebilmek için ilave çalışmalara gereksinim vardır. Biz bu duplikasyon mutasyonunun FMF patogenezinde gelecekte yapılacak araştırmalar için önemli bilgiler sağlayacağını düşünüyoruz.
Anahtar Kelimeler: FMF, MEFV Geni, Duplikasyon Mutasyonu, Tüm Ekzom Sekans Analizi

A Family From Turkey With 761_764dupCCGC p.Asn256Argfs70,c.761_764dupCCGC MEFV Gene Mutation, Their Clinical Features and Review of The Literature

ABSTRACT
Familial Mediterranean Fever (FMF) is an autosomal recessive hereditary disease that mainly affects Armenian, Jewish, Turkish and Arab populations and the most common and best understood periodic fever disease. The Mediterranean Fever (MEFV) gene is responsible for the disease. This gene including 10 exon and placed on chromosome 16p13.3. A family from Turkey with a total of five members clinically diagnosed as FMF are examined. All exom sequencing analysis of MEFV gene was done for all family members. According to our results, a 761_764dupCCGC (p.Asn256Argfs70,c.761_764dupCCGC) duplication mutation was detected in exon 2 of MEFV gene. Although our proband, his brother, sister and father have carried this mutation, the probands' mother has not any mutation. There is only one case with this mutation (HGMD no: CI055758) in the literature and limited information about clinical datas of the patient was shared. The proband has no family history of FMF but has chest and abdominal pain. Interestingly, the others family members with this mutation has no clinical findings for FMF. According to the PolyPhen-2 and Mutation Taster bioinformatics programs, this duplication seems to be pathogenic. Futher studies are needed to obtain more clear information about the 761_764dupCCGC mutation. We thought that this duplication mutation may give significant knowledge for future research on FMF pathogenesis.
Keywords: FMF, MEFV Gene, Duplication Mutation, Complete Exom Sequencing Analysis

INTRODUCTION

Familial Mediterranean Fever (FMF) (OMIM #249100) is an autosomal recessive hereditary autoinflammatory disease that initially affects Armenian, Jewish, Turkish and Arab populations, and the most common and best understood periodic recurrent attacks of fever and serositis with remerkable acute-phase inflammation (1). Renal amyloidosis, which can lead to renal failure is the most severe complication of FMF. The FMF gene is the Mediterranean Fever (MEFV) gene was identified in 1997. This gene to be composed of 10 exons, which placed on chromosome 16p13.3 and it is responsible for the disease and its protein product are named marenostrin/pyrin consisting of 781 amino acids. It was indicated that this protein has an significant role in the regulation of inflamation(2).

When the colchicine is not used, it was showed that chronic renal failure develops in the majority of patients with FMF around 40 years of age (3). Renal involvement initially manifests as proteinuria, and by stages progresses into nephrotic syndrome and goes to chronic renal failure. In a previous study, it was demonstrated that country of residence and M694V homozygosity in the MEFV gene are the leading risk factors for developing renal amyloidosis (4). Furthermore ethnicity, serum amyloid-associated (SAA)1 α/α genotype, male gender, having joint pain and family history of FMF have also been shown to increase the risk of developing amyloidosis (5,6).

Autosomal recessive pattern of inheritance is usually evident clinically but it has been reported that significant numbers of patients who had only one heterozygous mutation, clinicaly compatible with FMF and give well respons to colchicine were diagnosed (7). This syndrome shows a heterogeneous genetic basis.

MATERIAL AND METHODS

In this study, a Turkish non-consanguineous family with a total of five members clinically diagnosed as FMF are investigated. The DNA was isolated from peripheral blood samples of all individuals. All exons of MEFV gene (1,2,3,4,5,6,7,8,9,10) were amplified via PCR technic and whole exom sequencing analysis of MEFV gene was done for each family members.

RESULTS

As a result, a rare duplication mutation named 761_764dupCCGC p.Asn256Argfs70, c. 1_764dupCCGC in the coding region on exon 2 of MEFV gene was shown in the proband. Also this mutation was detected in probands' sister, brother and father. But this mutation was not detected in the probands' mother. Additionally, the clinical data of the family members were detected (Table 1).

Table 1 : Clinical data of the family members.

Cases	Age	Age at started symptoms	Fever	Recurrency of the attack	Abdominal pain	Chest pain	Arthrit	Erythema	Amyloidosis
Proband	6	3	-	Once in 2 months	+	+	-	-	-
Proband's brother	11	-	-	-	-	-	-	-	-
Proband's sister	15	-	-	-	-	-	-	-	-
Proband's father	41	-	-	-	-	-	-	-	-
Proband's mother	35	-	-	-	-	-	-	-	-

DISCUSSION

Molecular diagnostic testing for FMF is a non-invasive, high sensitive and specific method that used for the correct diagnosis before the emergence of all clinical symptomps of disease. In addition, by using of molecular genetic tests, FMF can be diagnosed early in pediatric patients and individuals who had atypical clinical findings (8). To date, more than 314 gene mutations and polymorphisms have been discovered in the MEFV gene (9). Still new mutations are identified and investigated for its' relation with FMF clinic (10).

In the current study, we aimed to contribute to the a rare duplication mutation 761_764dupCCGC spectrum datas. In our study, a duplication 761_764dupCCGCp.Asn256Argfs70,c.761_764dupC CGC mutation was detected in exon 2 of MEFV gene (Figure 1).

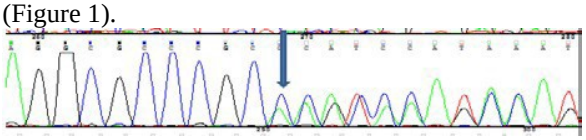

Figure 1: Nucleotide sequence of exon 2 of the MEFV gene showing a 761_764dupCCGC (p.Asn256Argfs70, c.761_764dupCCGC)duplication mutation in our proband.

The 761_764dupCCGC was first described in 2005 by Dr.Lohse (9) and it was shared limited information about clinical datas of the patient. It is said that the patient was from Turkish origin and had FMF-related symptoms. To the best of our knowledge, this was the second report of this mutation in the literature and both described cases with 761_764dupCCGC mutation in the literature were from Turkish origin. In spite of mutations and polymorphisms are frequent on exon 2 in the MEFV gene, this mutation seems to be a very rare mutation. In our current study, the clinical features of the disease such as age at started symptoms, fever, recurrency of the attack, abdominal pain, chest pain, arthrit, erythema and amyloidosis were investigated as detailed for all members of the family. Our results indicated that addition to our proband, his sister, brother and father have carried the mutation, too (Figure 2).

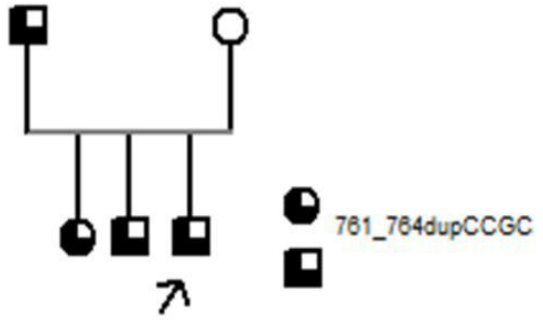

Figure 2: Family Pedigree of the proband.

Conversly, probands' mother has not carry a mutation on MEFV gene. The proband has no family history but has clinical findings of FMF such as abdominal, chest pain. Clinical data of the patients are shown in Table 1. Interestingly, excluding proband the other family members who carried this mutation has any clinical findings of FMF now. This situation may be caused from the differences of the related gene expression among family members. Colchicine therapy was started to the our proband and his answer to the colchicine will be followed by routine examinations. This family has been under clinical follow-up especially those who have no complaints yet and will be looked at the parameters such as erythrocyte-sedimentation rate, C-reactive protein, CBC (complete blood count), SAA (systemic amyloid AA) protein that can be associated with inflammation will be checked at regular intervals.

According to the PolyPhen-2 and Mutation Taster bioinformatics programs, the current duplication seems to be pathogenic. Because this duplication mutation formed a stop codon, a truncated protein is formed as a product of the related gene. It was required that the futher research are needed to obtain more accurate knowledge about the 761_764dupCCGC duplication mutation. Because of this mutation is a rare, depending on the increased number of individuals having this mutation, the exact effects of the mutations will be understood more easily. We thought that this duplication mutation may provide significant knowledge for future research on FMF pathogenesis and especially genotype-phenotype association studies.

At exon 2, four insertions have been reported so far and named as 334_335insG (p.Glu112fs*130), 390_391insGAGGGGAAC (p.Glu128_Asn130dup), 606_621dup (p.Ser208Alafs*39) and 761_764dupCCGC (p.Asn256Argfs*70) (9). Except 334_335insG (p.Glu112fs*130) mutation, these insertions have been associated with the FMF related symptoms. The 334-335 InsG causes a frameshift mutation and was identified in 2002 (9,11). According to datas as we reach, the patient who had this mutation had no symptomps related with FMF in this time. Additionally, the FMF clinic may be seen now but we could not get any information about it. The 334-335 InsGmutation identified in exon 2 from Greece (9), interestingly we had a family with 334-335 DelG mutation in exon 2 of the MEFV gene from Turkey and that was the first report of 334-335 DelG in exon 2 of the MEFV gene in the literature (12). In this family our proband and her mother had especially recurrent abdominal pain and our proband complained of joint pain. So they have used colchicine and they see significant benefit from colchicine also.

The proportion of FMF cases is larger in Eastern Mediterranean populations (especially in Turkish population). The Turkish population including more than 78 million resident has a big proportion of all the FMF cases in the World. The approximately calculated prevalence of FMF in Turkey 1 / 1.000 and an estimated carrier rate is set forth as 1/5 (1). Therefore, futher investigation is necessary to obtain more accurate data about the

disease for more effective and useful public health services. In our study, we report that a rare mutation of the MEFV gene from Turkish family. The detailed clinical features of the disease such as age at started symptoms, fever, recurrency of the attack, abdominal pain, chest pain, arthrit, erythema and amyloidosis were also researched for all members of the family. Additionally we showed an other rare mutation in exon 1 in a recent study although mutations and polymorphysms are very rare in exon 1 (13). So with all this information we can say that in Turkish society due to the high incidence of MEFV gene mutations looking through newborn screening will be discussed in the future. Similar study have also been available on this topic (14). Because of the MEFV heterogenity in Turkish FMF patients, larger serial analyses using different methods are necessary to detect the distribution of MEFV mutations and to determine genotype-phenotype associations.

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